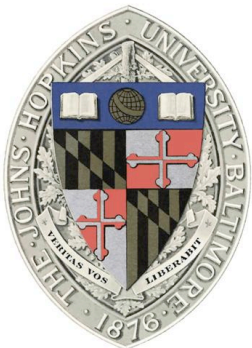# High-Resolution Diffusion Tensor Imaging and Clinical Applications

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Overview

- Anatomy of the hippocampus and the perforant path

- Role of the perforant path in encoding new memories

- High-resolution DTI methods and quantifying perforant path diffusion signal

- Perforant path DTI and hippocampal function

- Quantifying dendritic integrity using high-res DTI. Is it possible?
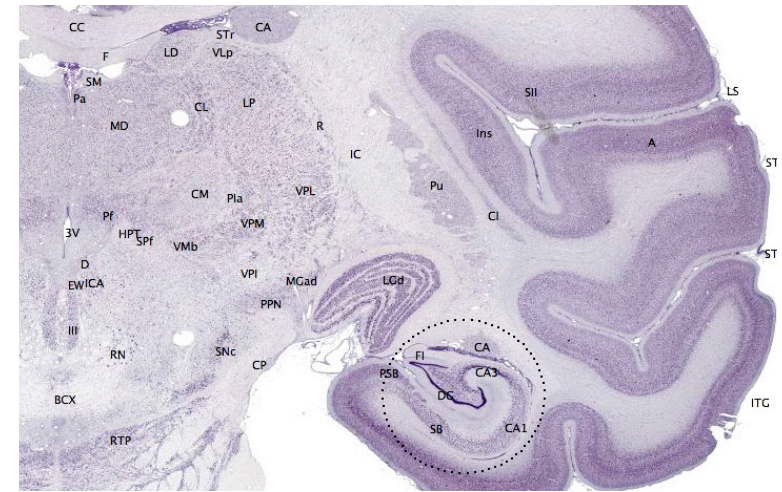
- Future directions

The hippocampus and perforant path
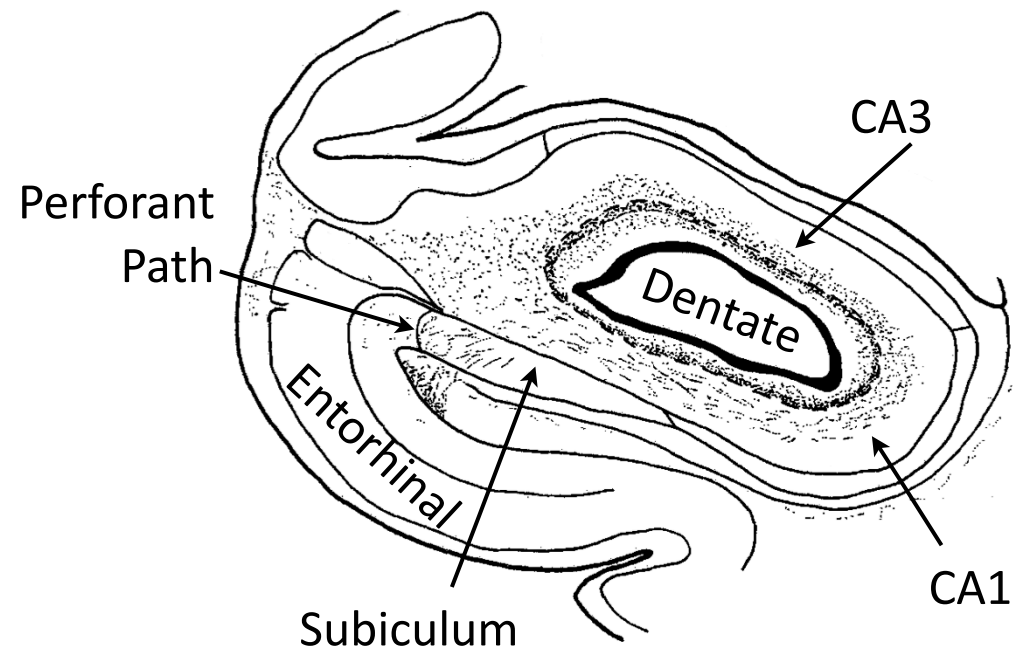
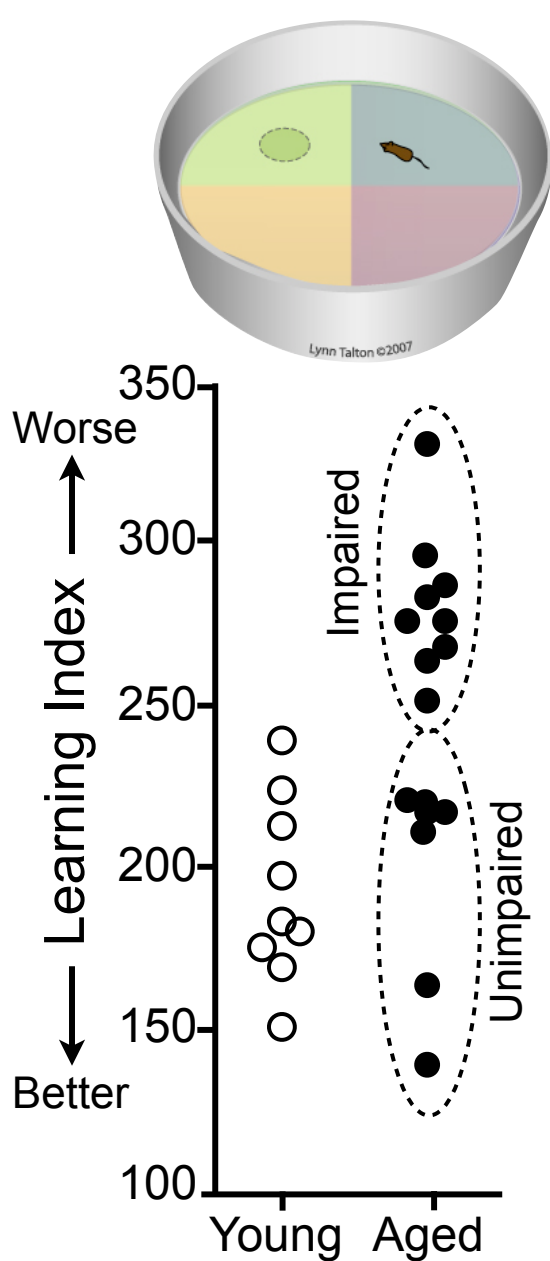## The rat hippocampus
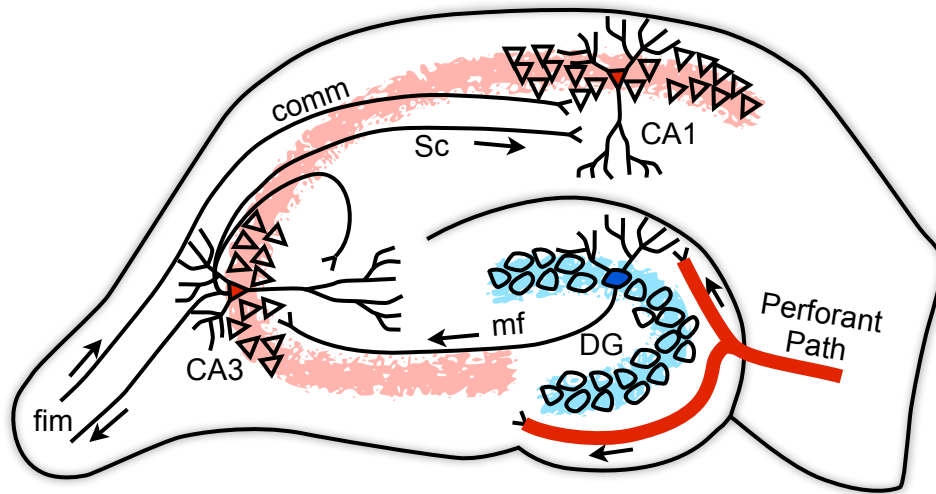
The primate hippocampus
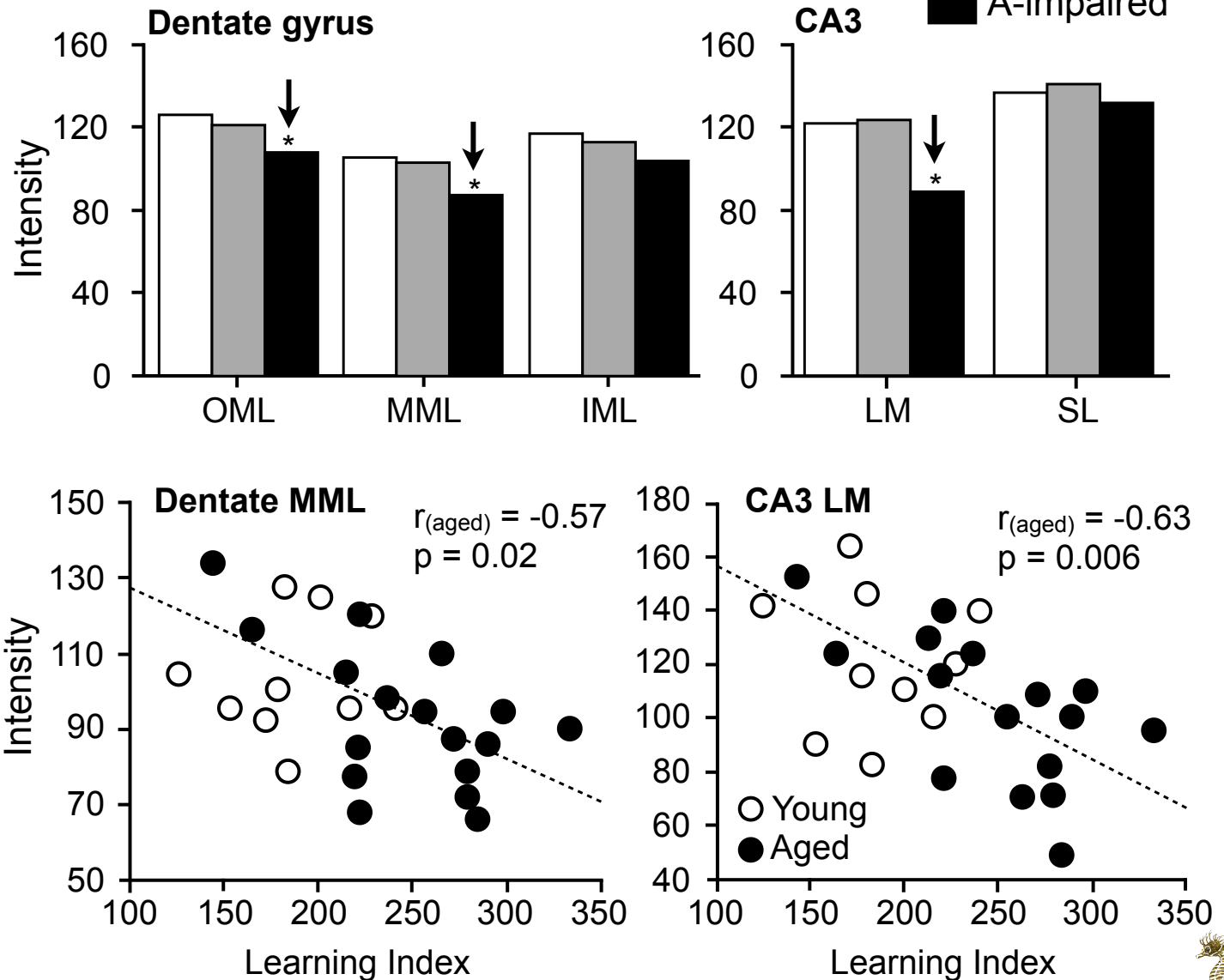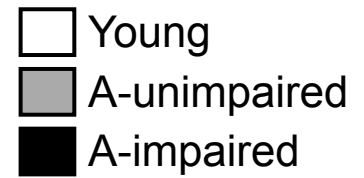

The perforant path

- Brings input from EC Layer II to the DG and CA3.

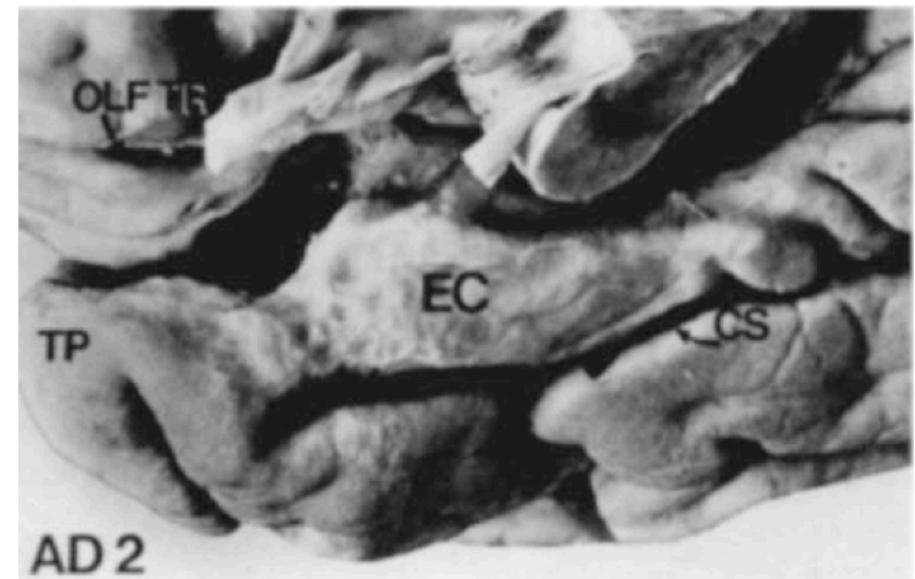- Necessary for normal memory function.

PP is necessary for normal memory

SYN-IR in PP terminal zones
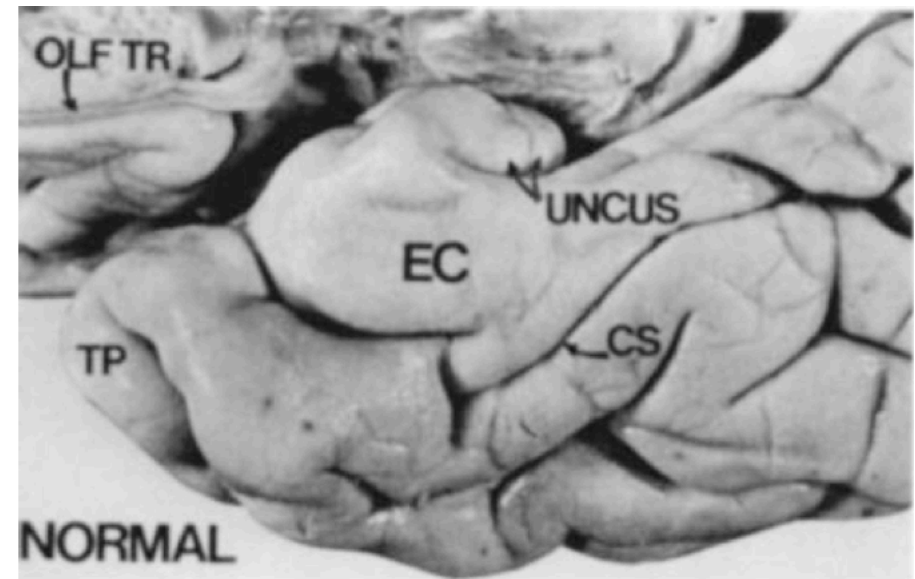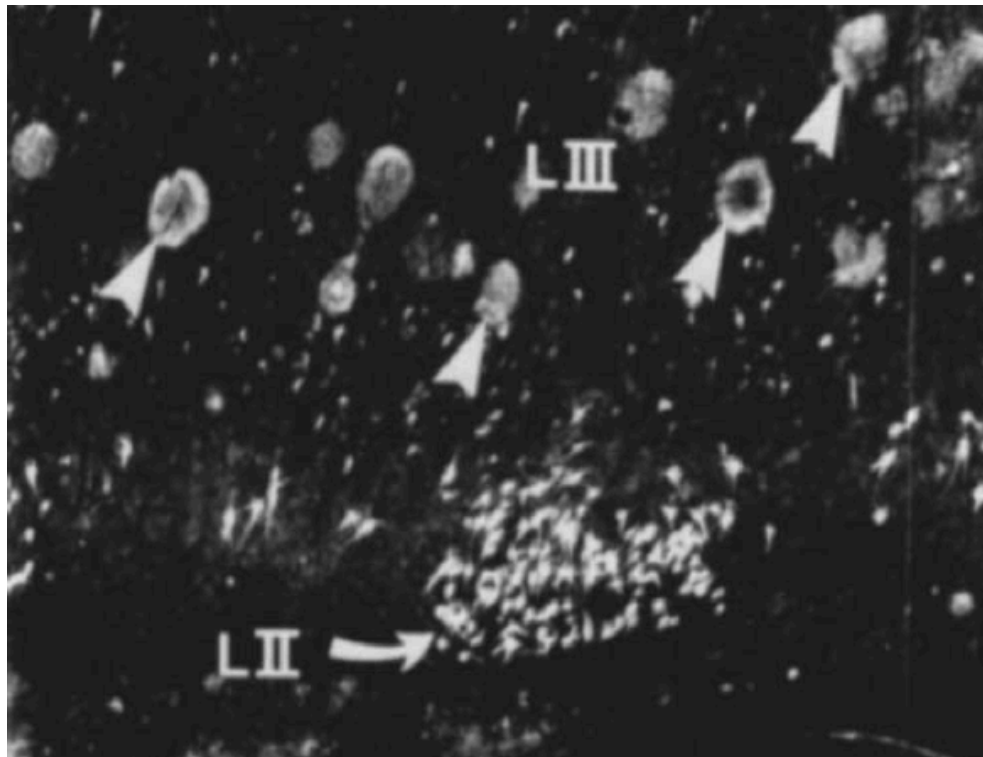
Young — A-unimpaired — A-impaired

Smith et al. *J Neurosci,* 2000

The perforant pathway in AD

- PP destroyed in Alzheimer's

- Massive cell loss in Layer II EC

- Tangle pathology

Hyman et al. *Hippocampus,* 1991

Motivation for PP imaging

- Suspect that it **changes slowly with aging** and that this change may predict **memory deficits** (shown in rats, but not in humans).

- We know it **changes dramatically in the course of Alzheimer's** but picking up earliest/subtle change may help us identify disease early → **potential biomarker**.
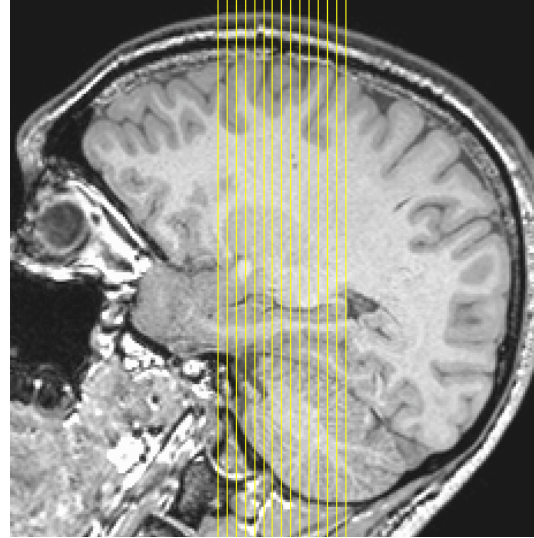
- **The Problem:**
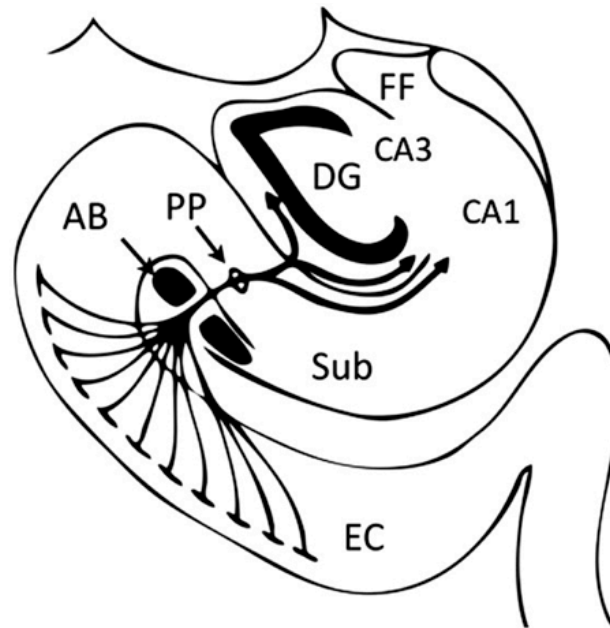
  ▸ Only a few mm thick

  ▸ Zone is rich with other fibers in the angular bundle

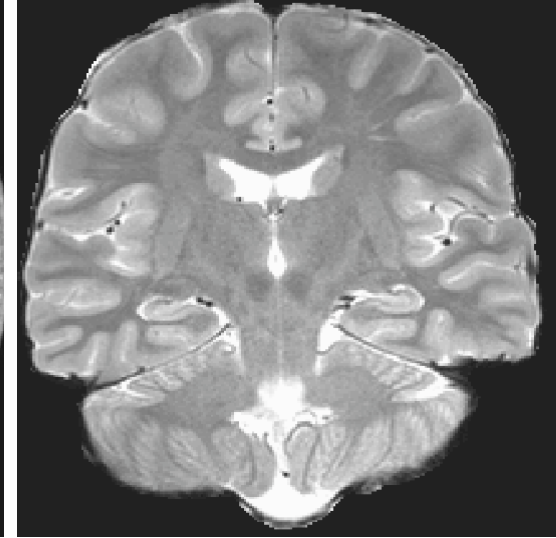 ▸ Problem for previous investigations

High-Resolution DTI Protocol

- 3T Philips with SENSE (r=2.5)

- 15 coronal slices

- Resolution: 0.66 x 0.66 x 3 mm

- 32 directions

- Flip angle = 90 deg

- TR/TE = 2,717 ms / 67 ms

- b = 1,200 s/mm^2

- Partial K = 60%
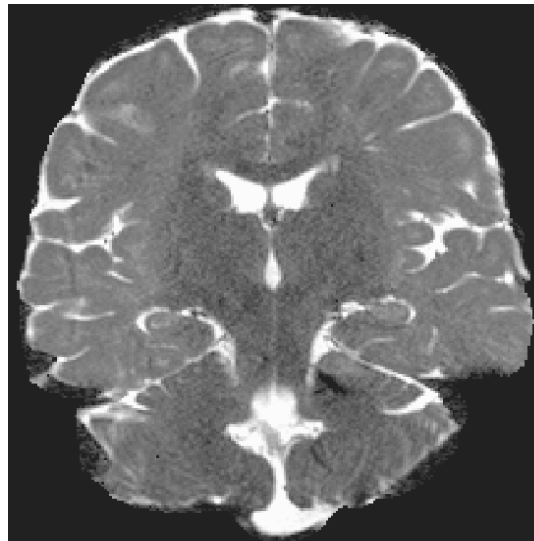
- 12 runs (4.5 mins each)
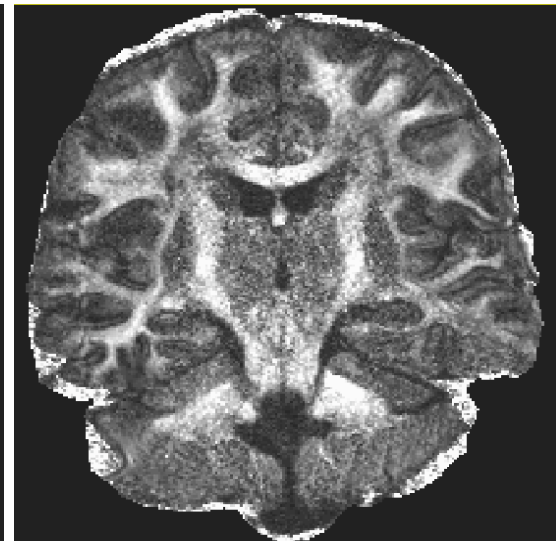
- Co-planar high-res T2 FSE

Hippocampal slab

T2 FSE

Mean B0

Mean FA map

Yassa M. , in *Handbooks of Alzheimer's Disease, Vol II: Imaging the Alzheimer Brain* (in press)

Processing and Analysis

- **FMRIB's Diffusion Toolbox (FSL FDT)**

  - Motion and eddy current correction

  - Tensor solving

  - Extract principal eigenvectors/eigenvalues and scalar maps

  - Bedpostx and Probtrackx for tractography

- **PPTool** (In-house software programmed in MATLAB)

  - Define canonical PP location based on anatomy

  - Quantify how well the principal EV correlates with this

$$PPproj = \frac{\left| \vec{p} \bullet \left(\vec{V_1} \times FA^2 \times L_1 \right) \right|}{\sqrt{\left(\vec{p} \bullet \vec{p} \right)}}$$

$\vec{p} =$ Perforant Path Direction
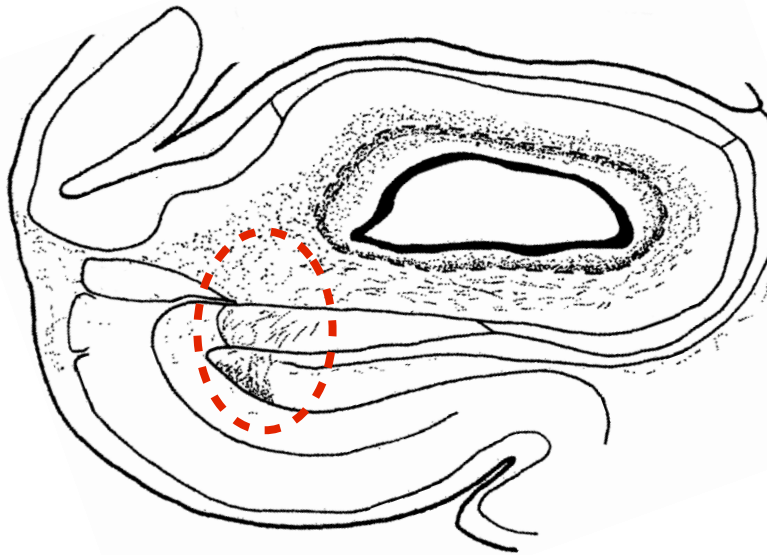
$\vec{V_1} =$ Principal Eigenvector

$L_1 =$ Principal Eigenvalue
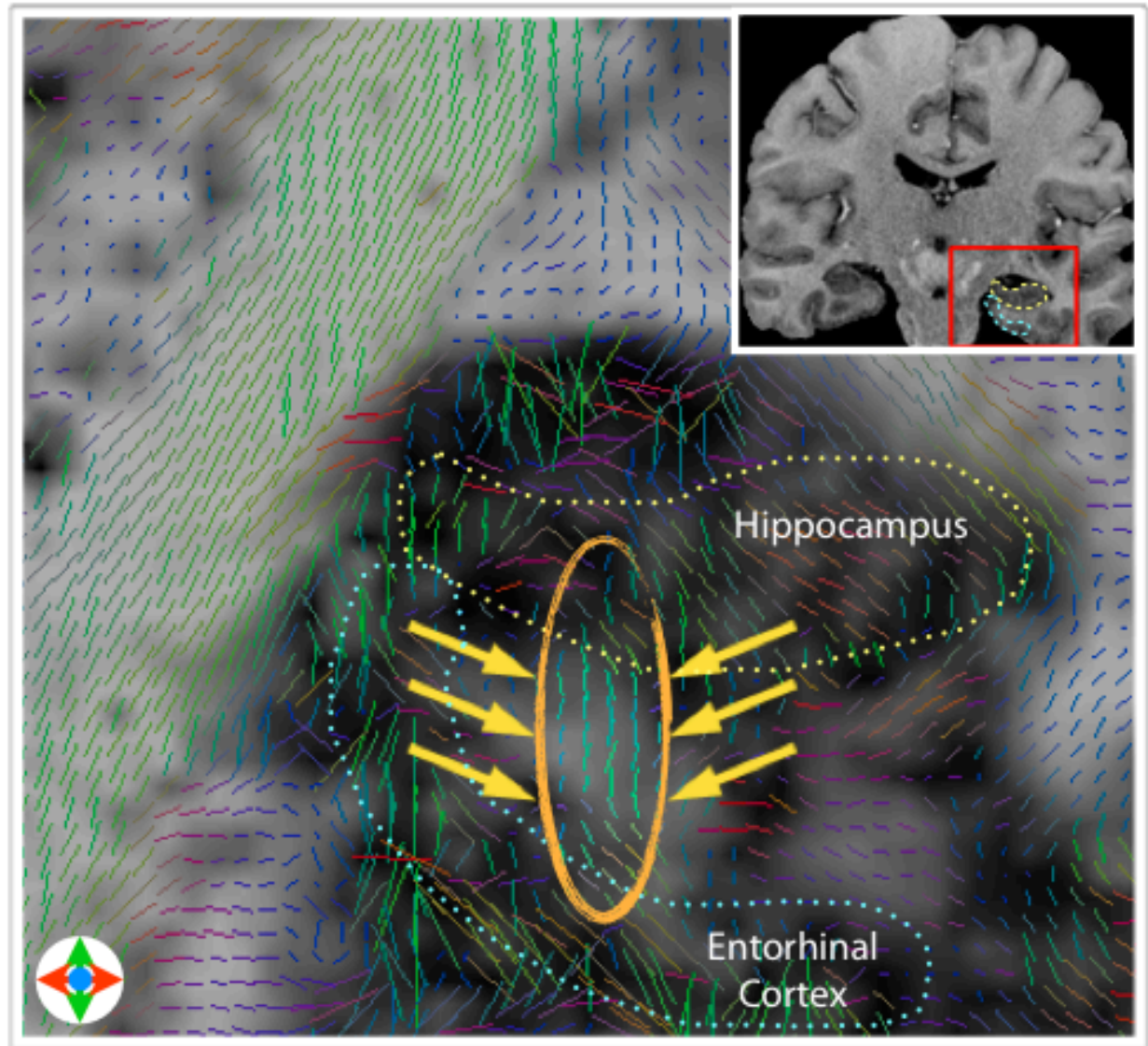
$FA =$ Fractional Anisotropy
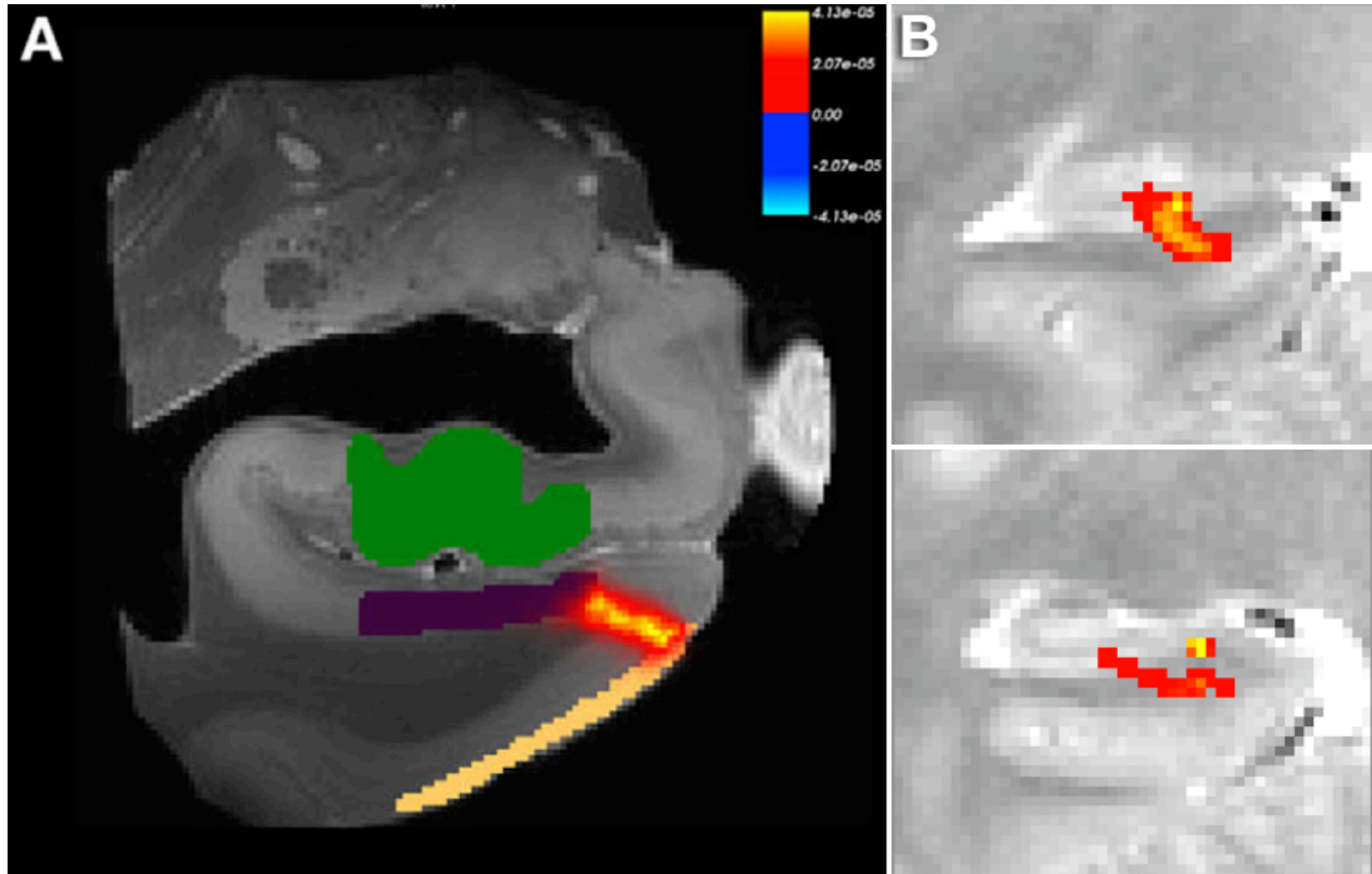
Visualizing the perforant path in vivo

High-res DTI Tensor visualization overlaid on FA map

Witter and Amaral, *J. Comp. Neurol.*, 1991

Yassa, Muftuler and Stark *PNAS,* 2010
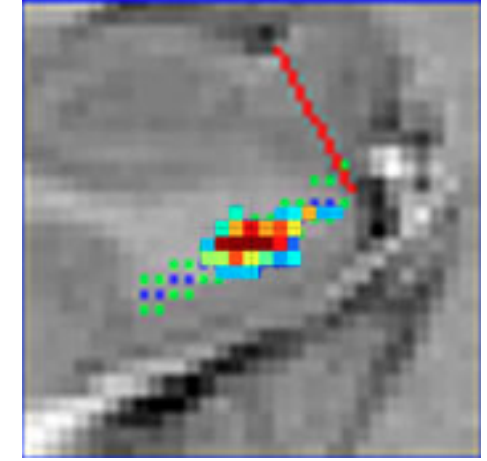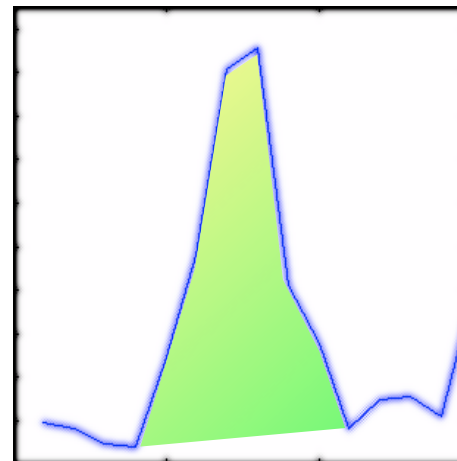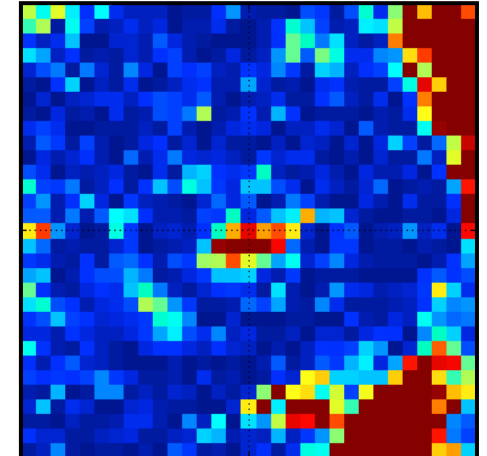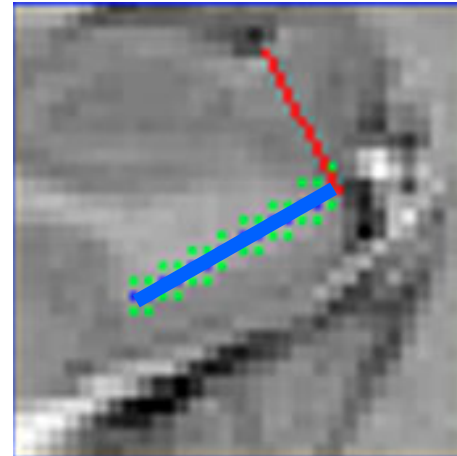
Tractography of the perforant path

Probabilistic tractography of the perforant path in *ex vivo* human tissue - 4.7 Tesla, 40 hours, 0.2 mm isotropic scan (Augustinack et al.,2010)

Replication *in vivo* using high-res DTI - 3 Tesla, 54 minutes, 0.6 x 0.6 x 3mm scan

Yassa M. , in *Handbooks of Alzheimer's Disease, Vol II: Imaging the Alzheimer Brain* (in press)
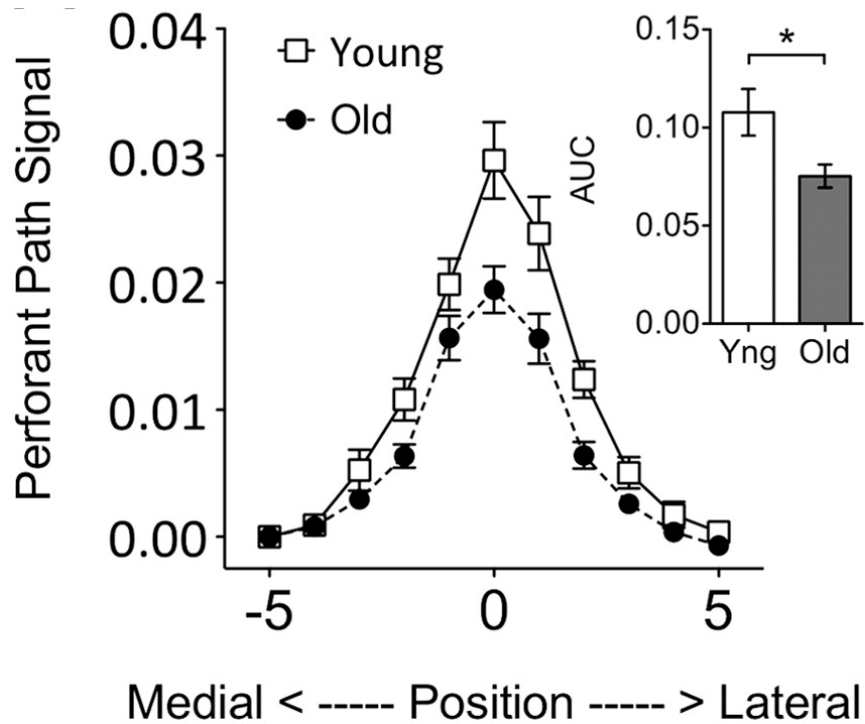
Quantifying the perforant path

$$PPproj = \frac{\left| \vec{p} \bullet \left(\vec{V_1} \times FA^2 \times L_1 \right) \right|}{\sqrt{\left(\vec{p} \bullet \vec{p} \right)}}$$

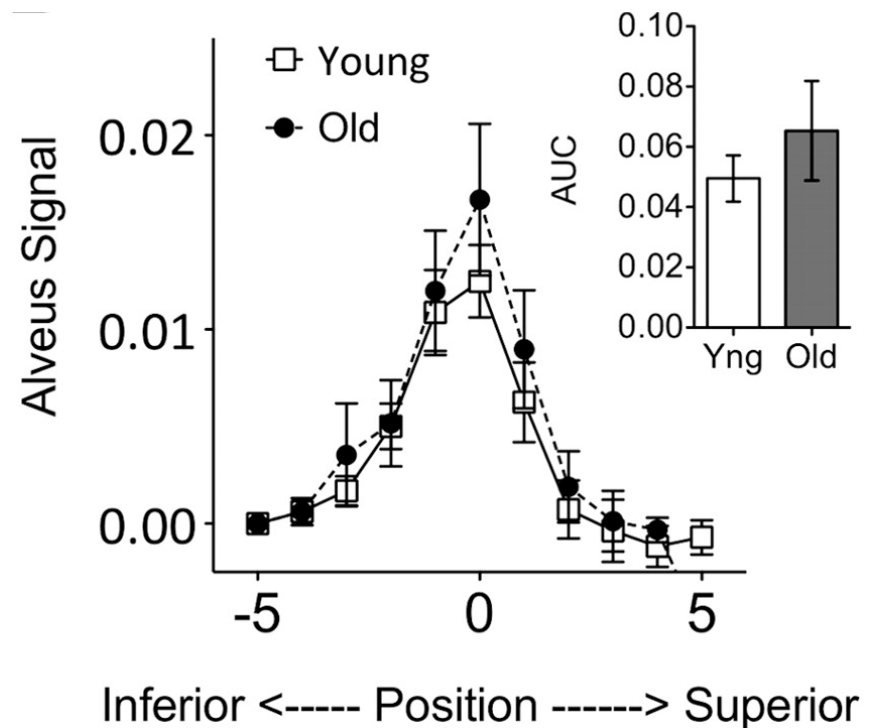*Operationalize PP signal as area under the curve*

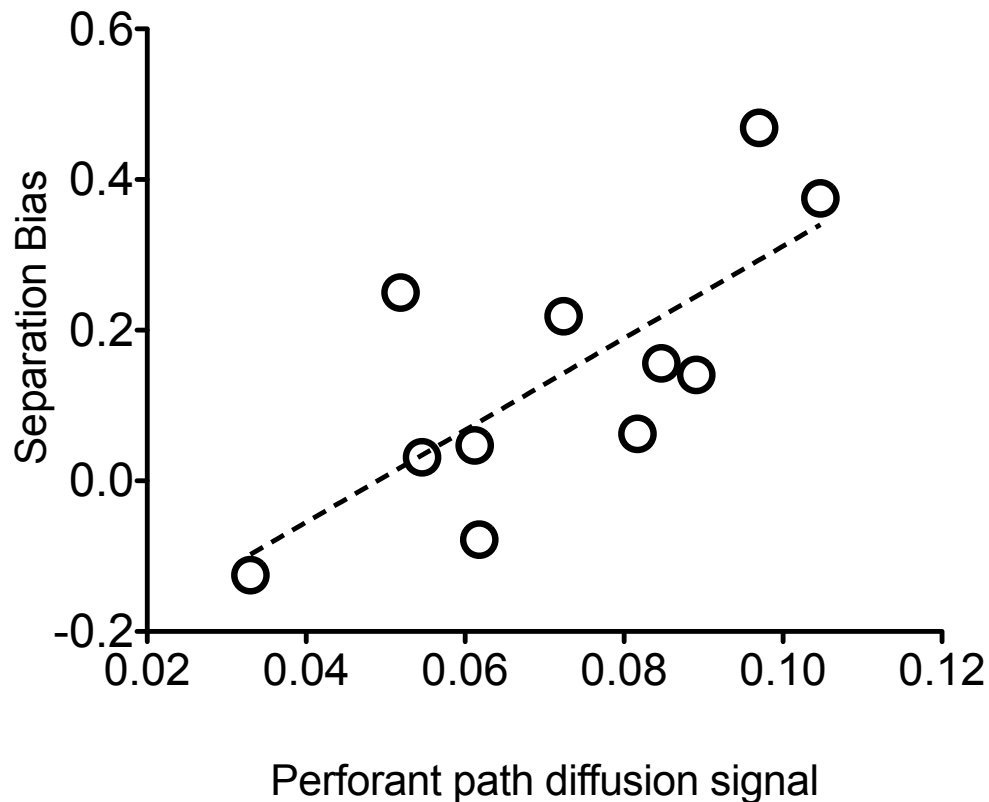# Degraded perforant path with aging

Perforant path

Control: Alveus
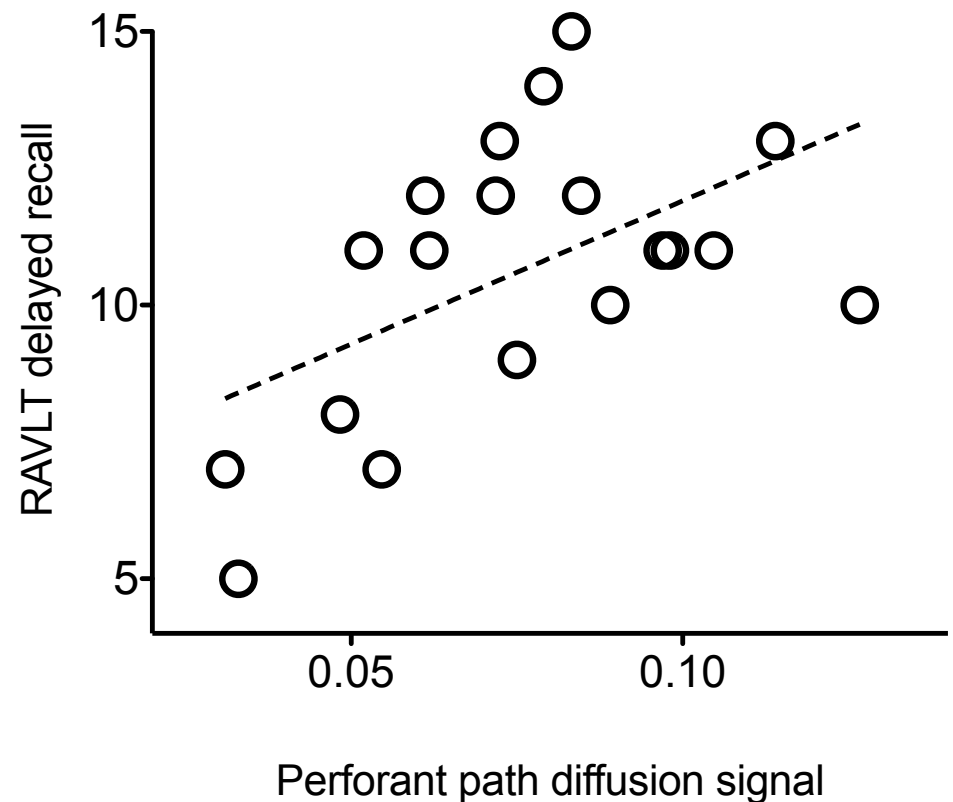
Relationship to memory

Mnemonic Discrimination

Word List Delayed Recall

Yassa, Muftuler and Stark *PNAS,* 2010; Yassa et al. *PNAS*, 2011

Interim summary

- Can use hi-res DTI to image and quantify the perforant path

- Perforant path diffusion signal changes with age and is linked to memory deficits.

- What about the **dendrites** in the molecular layer in CA3/DG? These are the synaptic targets of the perforant path.

- **Dendritic integrity** is thought to also degrade with age but has not been investigated. Can we use hi-res DTI to **image dendritic diffusion**?

- CA1 and CA3 pyramidal cells have **long apical dendrites** that are highly organized.
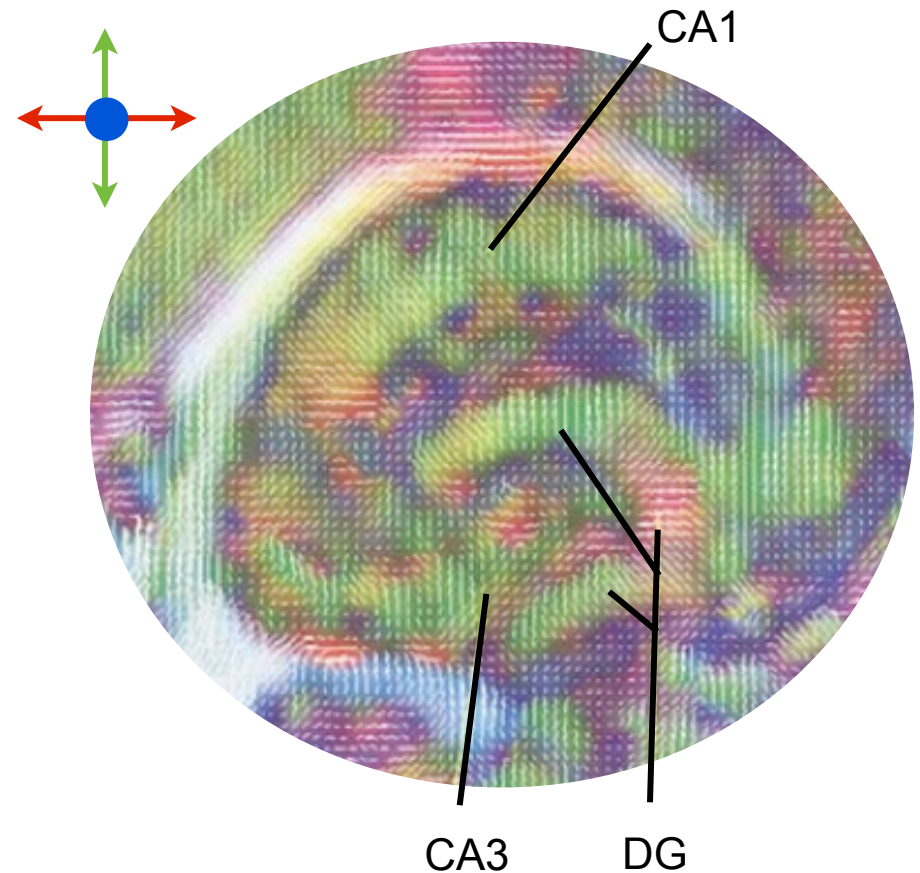
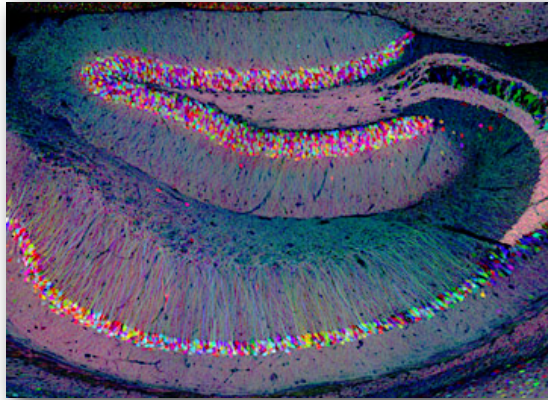# DTI can reveal dendritic organization

Golgi's hippocampus
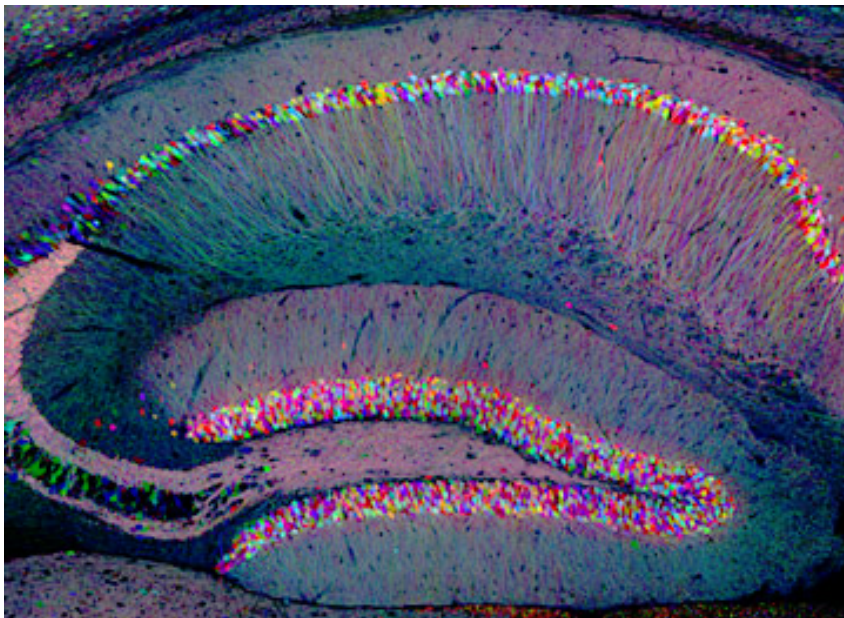
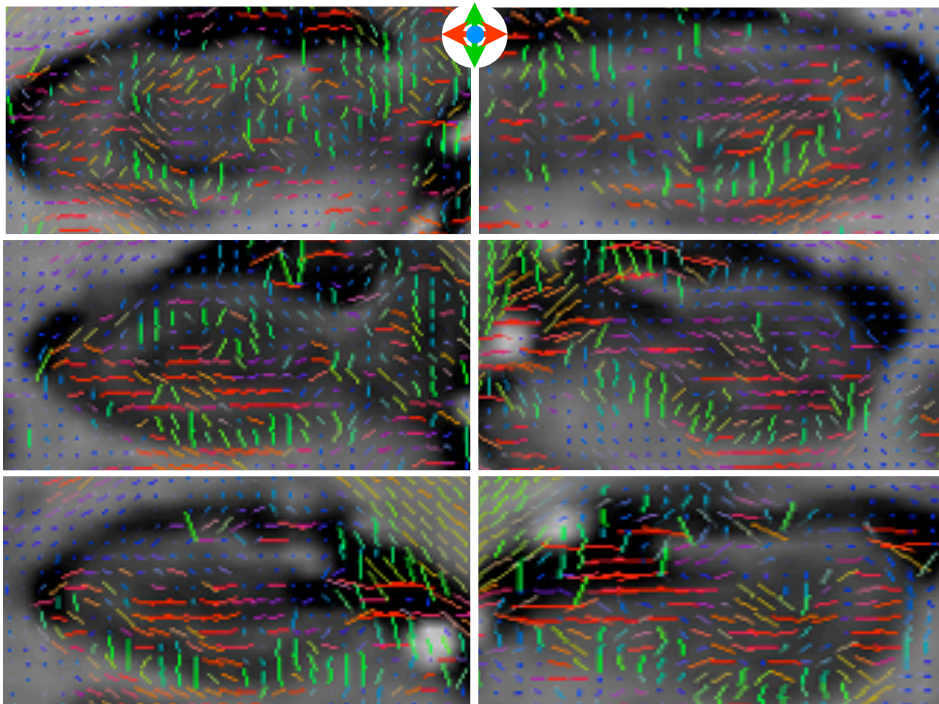"Brainbow" hippocampus
Courtesy of Tamily Weissman, Harvard.

CA1

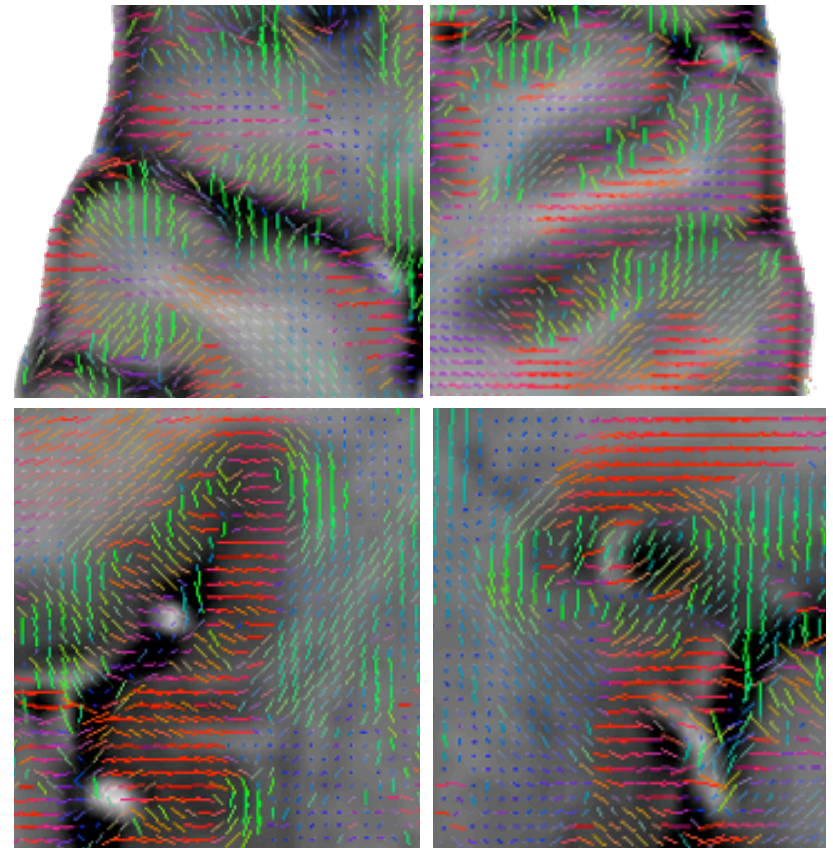CA3   DG

9.4 Tesla DTI of rodent hippocampus
Zhang et al. 2002

Hi-res DTI of dendritic fields

Cortical tensor maps

Hippocampal tensor maps

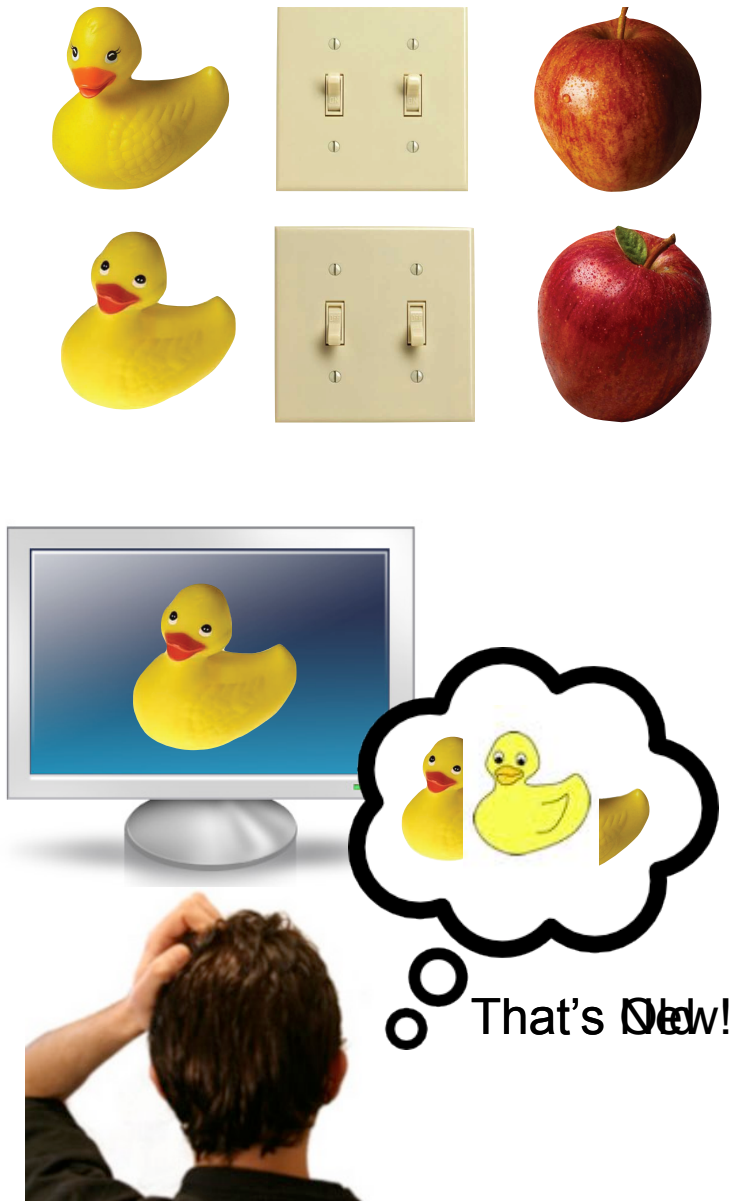Yassa, Muftuler and Stark *PNAS,* 2010

Dendritic FA is linked to CA3 function

Older Adults

CA3 GM FA (y-axis): 0.11, 0.12, 0.13, 0.14, 0.15

CA3 rigidity (failure to discriminate new items) (x-axis): -0.005, 0.000, 0.005, 0.010

That's New!
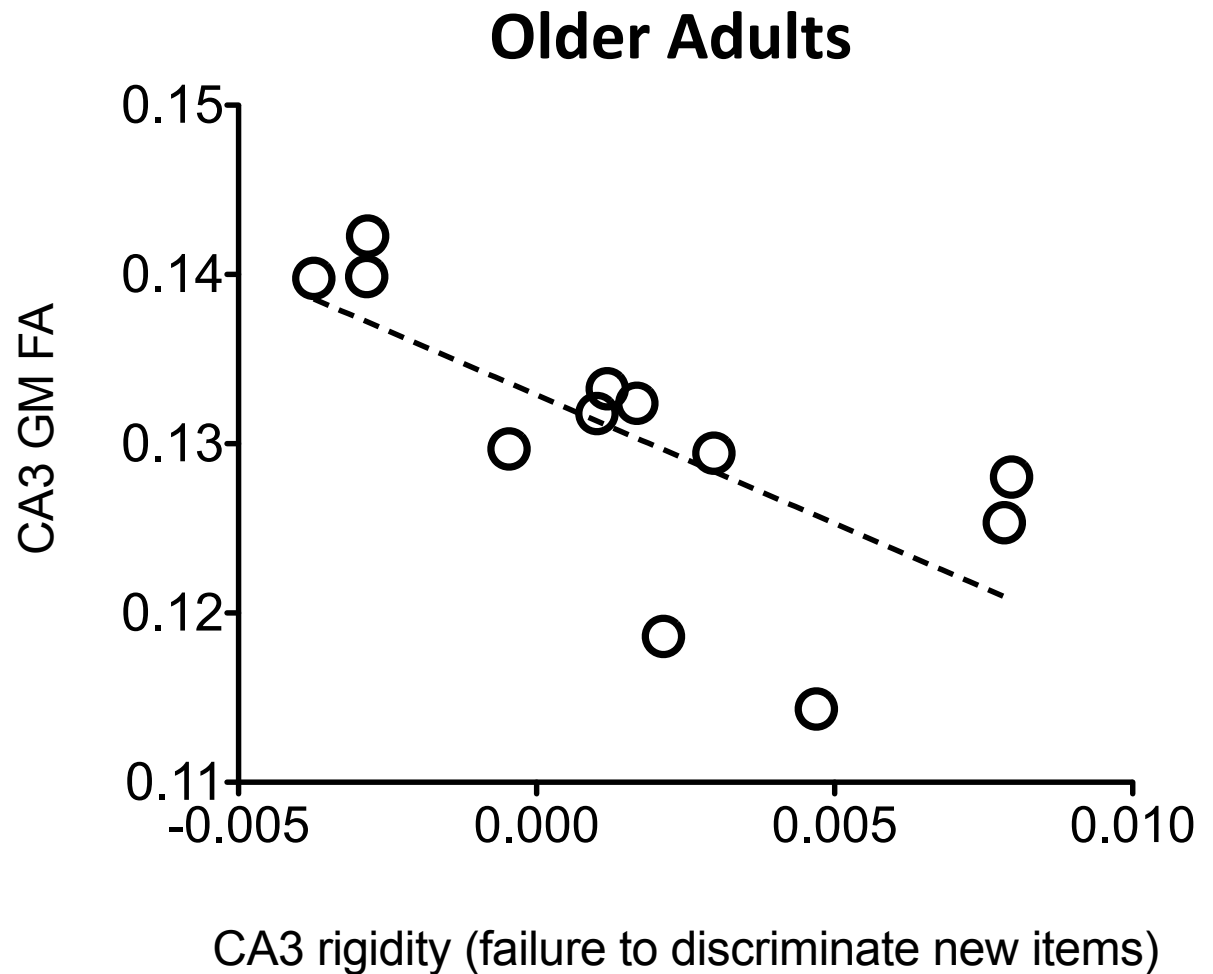
Biomarkers for cognitive decline?

- Can be extended to **Alzheimer's disease** both as biomarkers for early diagnosis and as outcome measures for interventions.

- Still have issues with **standardization** across scanners and across sites → critical for large scale clinical trials.

- DTI may not be the best tool for perforant path. **DSI/HARDI** may be better suited for this.

- Validation with post-mortem **histology**.

- So far the data has been promising, but we have a long way to go!

Acknowledgments

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- Joe Watabe

http://learnmem.jhu.edu